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(54) Title: 2-[5-(5-CARBAMIMIDOYL-1H-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL]-SUCCINIC ACID DERIVATIVES AS FACTOR VIIA INHIBITORS

(57) Abstract: The present invention relates to novel inhibitors of Factors VIIa, IXa, Xa, XIa, in particular Factor VIIa, pharmaceutical compositions comprising these inhibitors, and methods for using these inhibitors for treating or preventing thromboembolic disorders. Processes for preparing these inhibitors are also disclosed.

2-[5-(5-CARBAMIMIDOYL-1*H*-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL]-SUCCINIC ACID DERIVATIVES AS FACTOR VIIA INHIBITORS

BACKGROUND OF THE INVENTION

Field of invention

The present invention relates to novel inhibitors of Factors VIIa, IXa, Xa, XIa, in particular Factor VIIa, pharmaceutical compositions comprising these inhibitors, and methods for using these inhibitors for treating or preventing thromboembolic disorders. Processes for preparing these inhibitors are also disclosed.

State of the Art

Thrombosis results from a complex sequence of biochemical events, known as the coagulation cascade. A triggering event in coagulation is the binding of the serine protease Factor VIIa (FVIIa) found in the circulation, to tissue factor (TF), a receptor which is found on the surface of blood vessels after damage or inflammation. Once bound to TF, Factor VIIa catalyzes the formation of the serine protease Factor Xa, which subsequently forms the final protease in the cascade, thrombin.

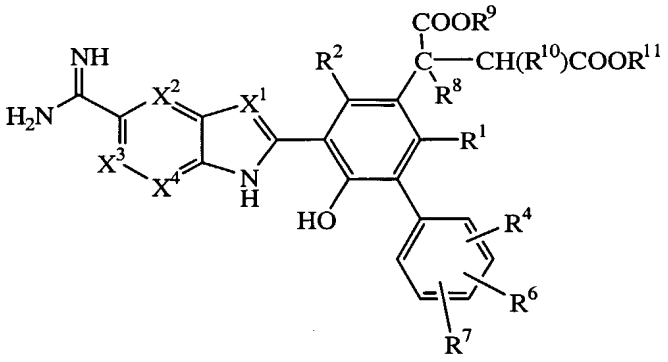
The clinical manifestations of thrombosis range from acute myocardial infarction (AMI or heart attack) and unstable angina (UA) which occur in the key blood vessels of the heart (coronary vasculature) to deep vein thrombosis (DVT) which is the formation of blood clots in lower extremities which often follows orthopedic surgery on the hip and knee, as well as general abdominal surgery and paralysis. Formation of DVT is a risk factor for the development of pulmonary embolism (PE) in which part of a blood clot formed in the lower extremities, breaks off and travels to the lung where it blocks the flow of blood. The unpredictable development of PE often leads to a fatal outcome. Thrombosis can also be generalized systemically, with microclot formation occurring throughout the vascular system. This condition, known as disseminated intravascular coagulation (DIC), can be a consequence of certain viral diseases such as Ebola, certain cancers, and sepsis. Severe DIC can lead to a dramatic reduction in the coagulation factors due to the excessive activation of the clotting response which may result in multiple organ failure, hemorrhage and death.

The formation or embolization of blood clots in the blood vessels of the brain is the key event resulting in ischemic stroke. Triggering factors that lead to stroke are atrial fibrillation or abnormal rhythm of the atria of the heart and atherosclerosis followed by thrombosis in the

main artery leading from the heart to the brain (carotid artery). Over 600,000 individuals suffer strokes each year in the U.S. Two-thirds of these stroke victims suffer some disability, and one-third suffer permanent and severe disability. Accordingly, there is a need for antithrombotic agents for the treatment of a variety of thrombotic conditions. The present invention fulfills this and related needs.

SUMMARY OF THE INVENTION

In one aspect this invention is directed to a compound of Formula I:



I

wherein:

X^1, X^2, X^3, and X^4 are independently –N- or -CR^5- wherein R^5 is hydrogen, alkyl, or halo with the proviso that not more than three of X^1, X^2, X^3 and X^4 are –N-;

R^1 and R^2 independently are hydrogen, alkyl, or halo;

R^4 is hydrogen, alkyl, alkylthio, halo, alkoxy, or nitro;

R^6 is hydrogen, alkyl, or halo;

R^7 is hydrogen, alkyl, halo, nitro, alkoxy, haloalkyl, haloalkoxy, hydroxyalkyl, carboxy, amino, alkylamino, dialkylamino, carbamimidoyl, alkylsulfonylamino, alkylthio, or ureido provided that at least one of R^4, R^6 and R^7 is not hydrogen;

R^8 is hydrogen, hydroxy, or alkyl;

R^{10} is hydrogen or alkyl; or

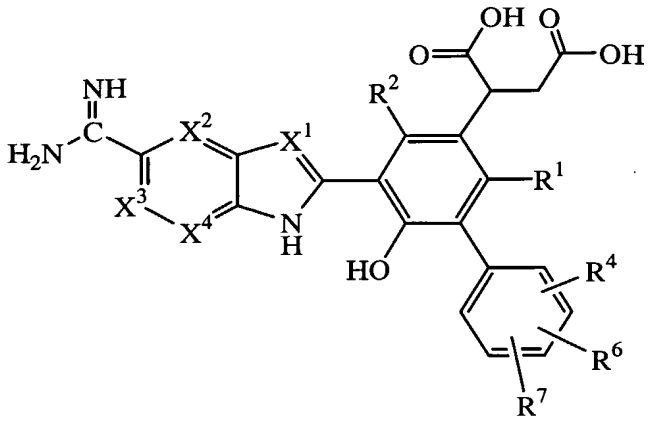
R^8 and R^{10} together form a covalent bond;

R^9 and R^{11} are independently hydrogen or alkyl; and

individual isomers, mixture of isomers, or a pharmaceutically acceptable salt thereof.

Preferably, R^7 is hydrogen, alkyl, halo, nitro, alkoxy, haloalkyl, carboxy, amino, alkylamino, dialkylamino, carbamimidoyl, alkylsulfonylamino, alkylthio, or ureido.

In a second aspect, this invention is directed to a compound of Formula II:



II

wherein:

X^1, X^2, X^3 and X^4 are selected –N- or -CR^5-, wherein R^5 is hydrogen, methyl or halo; with the proviso that not more than three of X^1, X^2, X^3 and X^4 represent N;

R^1 and R^2 independently are hydrogen, methyl or halogen; and

R^4, R^6 and R^7 are independently of each other hydrogen, hydroxy, methoxy, aminocarbonyl, methyl, isopropyl, acetyl, nitro or halogen, provided that none of R^4, R^5, and R^6 are attached to the C-4 position of the phenyl ring and also when only one of R^4, R^5, and R^6 is hydrogen, then the remaining of R^4, R^5, and R^6 are not located at the C-3 and C-5 position of the phenyl ring at the same time, the carbon attaching the phenyl ring to the rest of the molecule being the C-1 position; and

individual isomers and mixtures of isomers; or a pharmaceutically acceptable salts thereof.

In a third aspect, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I or II or a pharmaceutically acceptable salt thereof.

In a fourth aspect, this invention is directed to a method of treating a disease in an animal mediated by Factors VIIa, IXa, Xa and/or XIa, preferably VIIa, which method comprises administering to said animal a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I or II or a pharmaceutically acceptable salt thereof. The pharmaceutical composition can contains individual isomers or mixture of isomers of a compound of Formula I or II. Preferably, the disorder is a thromboembolic disorder or cancer, more preferably a thromboembolic disorder.

In a fifth aspect, this invention is directed to a method of treating a thromboembolic disorder in an animal which method comprises administering to said animal a pharmaceutical

composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I or II or a pharmaceutically acceptable salt thereof in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, a factor IXa, a factor Xa inhibitor, Aspirin® or Plavis®.

In a sixth aspect, this invention is directed to a method for inhibiting the coagulation of a biological sample (e.g., stored blood products and samples) comprising the administration of a compound of Formula I or II.

In a seventh aspect, this invention directed to the use of a compound of Formula I or II in the preparation of a medicament for use in the treatment of a thromboembolic disorder in an animal.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following terms, as used in the present specification and claims, are intended to have the meaning as defined below, unless indicated otherwise.

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

"Alkylthio" means a radical -SR where R is alkyl as defined above, e.g., methylthio, ethylthio, propylthio (including all isomeric forms), butylthio (including all isomeric forms), and the like.

"Amino" means a radical -NH_2.

"Alkylamino" means a radical –NHR where R is alkyl as defined above, e.g., methylamino, ethylamino, *n*-, *iso*-propylamino, *n*-, *iso*-, *tert*-butylamino, methylamino-N-oxide, and the like.

"Alkylsulfonylamino" means a radical –$NHSO_2R$ where R is alkyl as defined above e.g., methylsulfonylamino, ethylsulfonylamino, *n*- or *iso*-propylsulfonylamino, and the like.

"Alkoxy" means a radical -OR where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

"Dialkylamino" means a radical –NRR' where R and R' are independently alkyl as defined above, e.g., dimethylamino, diethylamino, methylpropylamino, methylethylamino, *n*-, *iso*-, or *tert*-butylamino, and the like.

"Carbamimidoyl" means a radical –$C(=NH)NH_2$.

"Halo" means fluoro, chloro, bromo, and iodo, preferably fluoro or chloro.

"Haloalkyl" means alkyl substituted with one or more halogen atoms, preferably one to three halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_3$, $-CHF_2$, and the like.

"Haloalkoxy" means a radical -OR where R is haloalkyl as defined above, e.g., $-OCH_2Cl$, $-OCF_3$, $-OCHF_2$, and the like.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

The present invention also includes the prodrugs of compounds of Formula I or II. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient of Formula I or II, when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or *in vivo*. Prodrugs of compounds of Formula I or II include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula I or II, and the like. Prodrugs of compounds of Formula I or II are also within the scope of this invention.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I or II. For example, when compounds of Formula I or II contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art.

Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure

of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid,

4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. Many geometric isomers of olefins, C=C double bonds, and the like can be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure (representing a compound of Formula I or II) are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

Certain compounds of Formula I or II exist in tautomeric equilibrium. Compounds of Formula I or II, which exist as tautomers are named, illustrated or otherwise described in this

application as one possible tautomer. However, it is to be understood that all possible tautomers are meant to be encompassed by such names, illustrations and descriptions and are within the scope of this invention. Additionally, as used herein the terms alkyl includes all the possible isomeric forms of said alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl, heteroaryl, heterocycloalkyl are substituted, they include all the positional isomers albeit only a few examples are set forth.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycloalkyl group optionally mono- or di-substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycloalkyl group is mono- or disubstituted with an alkyl group and situations where the heterocycloalkyl group is not substituted with the alkyl group.

A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

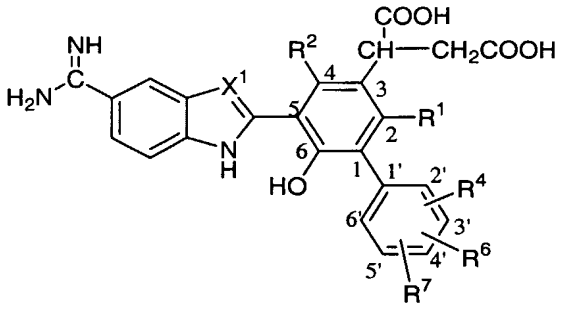
(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound of Formula I or II that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

"Ureido" means a radical $-NHCONH_2$ or a protected derivative thereof.

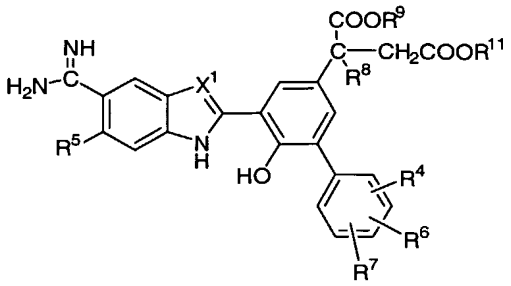
Representative compounds of Formulae I and II are:

Table I



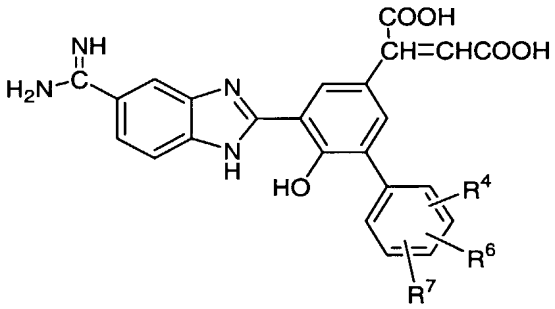
Cpd #	X^1	R^1	R^2	R^4	R^6	R^7
1	C	H	H	H	H	3'-NO_2
2	N	H	H	H	H	3'-NO_2
3	N	H	H	H	H	3'-(isopropyl)
4	N	H	H	H	H	H
7	N	H	H	H	H	3'-Cl
8	N	H	H	H	H	3'-OCH_3
9	N	H	H	H	H	3'-CH_3
10	N	H	H	2'-OCH_3	H	H
11	N	H	H	2'-Cl	3'-Cl	5'-Cl
12	C	H	H	H	H	3'-Cl
13	N	H	H	H	H	2'-F
14	N	H	H	2'-OCH_3	H	5'-F
15	N	H	H	2'-OCH_3	H	5'-OCH_3
16	N	H	H	H	H	3'-NH_2
17	N	H	H	2'-OCH_3	H	5'-NO_2
18	N	H	H	2'-NO_2	H	H
19	N	H	H	H	H	2'-CH_3
20	N	H	H	H	H	2'-NH_2
21	N	H	H	2'-Cl	H	5'-Cl
22	N	H	H	2'-OCH_3	H	6'-OCH_3
23	N	H	H	2'-OCH_3	H	5'-$CH(CH_3)_2$
24	N	H	H	H	H	2'-SCH_3
25	N	H	H	2'-Cl	H	3'-Cl
26	N	H	H	3'-Cl	4'-F	H
27	N	H	H	3'-F	5'-F	H
28	N	H	H	2'-SCH_3	H	5'-Br
29	C	H	H	H	H	3'-NH_2
30	C	H	H	H	H	3'-$NHCONH_2$
31	N	H	H	3'-CH_3	4'-CH_3	H

Table II



Cpd #	X^1	R^5	R^4	R^6	R^7	R^8	R^9	R^{11}
1	C	H	3'-NO_2	H	H	H	CH_2CH_3	CH_2CH_3
2	C	H	3'-NO_2	H	H	H	CH_3	CH_3
5	N	F	3'-NO_2	H	H	H	H	H

Table III



Cpd #	Isomerism around carbon-carbon double bond	R^4	R^6	R^7
1	Cis	2'-OCH_3	5'F	H

and are named as:

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-isopropyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',3',5'-trichloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2'-fluoro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2',5'-dimethoxy-biphenyl-3-yl]-succinic acid;

2-[3'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-5'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methyl-biphenyl-3-yl]-succinic acid;

2-[2'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',5'-dichloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',6-dimethoxy-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2'-methoxy-6-hydroxy-5'-isopropyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methylthio-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2',3'-dichloro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-chloro-5'-fluorobiphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3',5'-difluoro-biphenyl-3-yl]-succinic acid;

2-[5'-bromo-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methylthio-biphenyl-3-yl]-succinic acid;

2-[3'-amino-5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-ureido-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3',4'-dimethyl-biphenyl-3-yl]-succinic acid;

diethyl 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinate;

dimethyl 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinate;

2-[5-(5-carbamimidoyl-6-fluoro-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid; and

(Z)-2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6-hydroxy-2'methoxy-biphenyl-3-yl]-but-2-enedioic acid.

The compounds of Formulae I and II and the intermediates and starting materials used in their preparation are named generally by AutoNom 4.0 (Beilstein Information Systems, Inc.).

Preferred Embodiments

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula I are preferred. For example, a preferred group of compounds is that wherein:

R^7 is alkyl, halo, nitro, alkoxy, haloalkyl, carboxy, amino, alkylamino, dialkylamino, carbamimidoyl, alkylsulfonylamino, alkylthio, or ureido; and

when two of R^4, R^6 and R^7 are hydrogen, then the remaining of R^4, R^6 and R^7 is not located at the 4'-position of the phenyl ring with the carbon atom attaching the phenyl ring to the rest of the molecule being the 1'-position; and also when one of R^4, R^6 and R^7 is hydrogen, then the remaining of R^4, R^6 and R^7 are not simultaneously at the 3'- and 5'-position of the phenyl ring.

Within this group of compounds:

A more preferred group of compounds is that wherein:

X^1 is –N- and X^2, X^3, and X^4 are $–CR^5$- where R^5 is hydrogen.

Another more preferred group of compounds is that wherein:

X^1 is –N-; X^2 and X^4 are $–CR^5$- where R^5 is hydrogen and X^3 is $–CR^5$- where R^5 is halo, preferably fluoro or chloro.

Yet another more preferred group of compounds is that wherein:

X^1 is –C- and X^2, X^3, and X^4 are $–CR^5$- where R^5 is hydrogen.

Another more preferred group of compounds is that wherein:

X^1 is –C-; X^2 and X^4 are $–CR^5$- where R^5 is hydrogen and X^3 is $–CR^5$- where R^5 is halo, preferably fluoro or chloro.

Within the above preferred and more preferred groups, an even more preferred group of compounds is that wherein R^1 and R^2 are hydrogen; R^8 and R^{10} are hydrogen; and R^9 and R^{11} are hydrogen or ethyl, preferably hydrogen.

Within the above preferred and more preferred groups, another even more preferred group of compounds of Formula I is that wherein R^1 and R^2 are hydrogen; R^8 and R^{10} together from a covalent bond; and R^9 and R^{11} are hydrogen or ethyl, preferably hydrogen.

Within the above preferred and more preferred groups, a particularly preferred group of compounds of Formula I is that wherein:

R^4 and R^6 are hydrogen and R^7 is located at the 3'-position of the phenyl ring. Preferably, R^7 is nitro or halo, more preferably nitro, chloro, or fluoro, most preferably nitro.

GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to

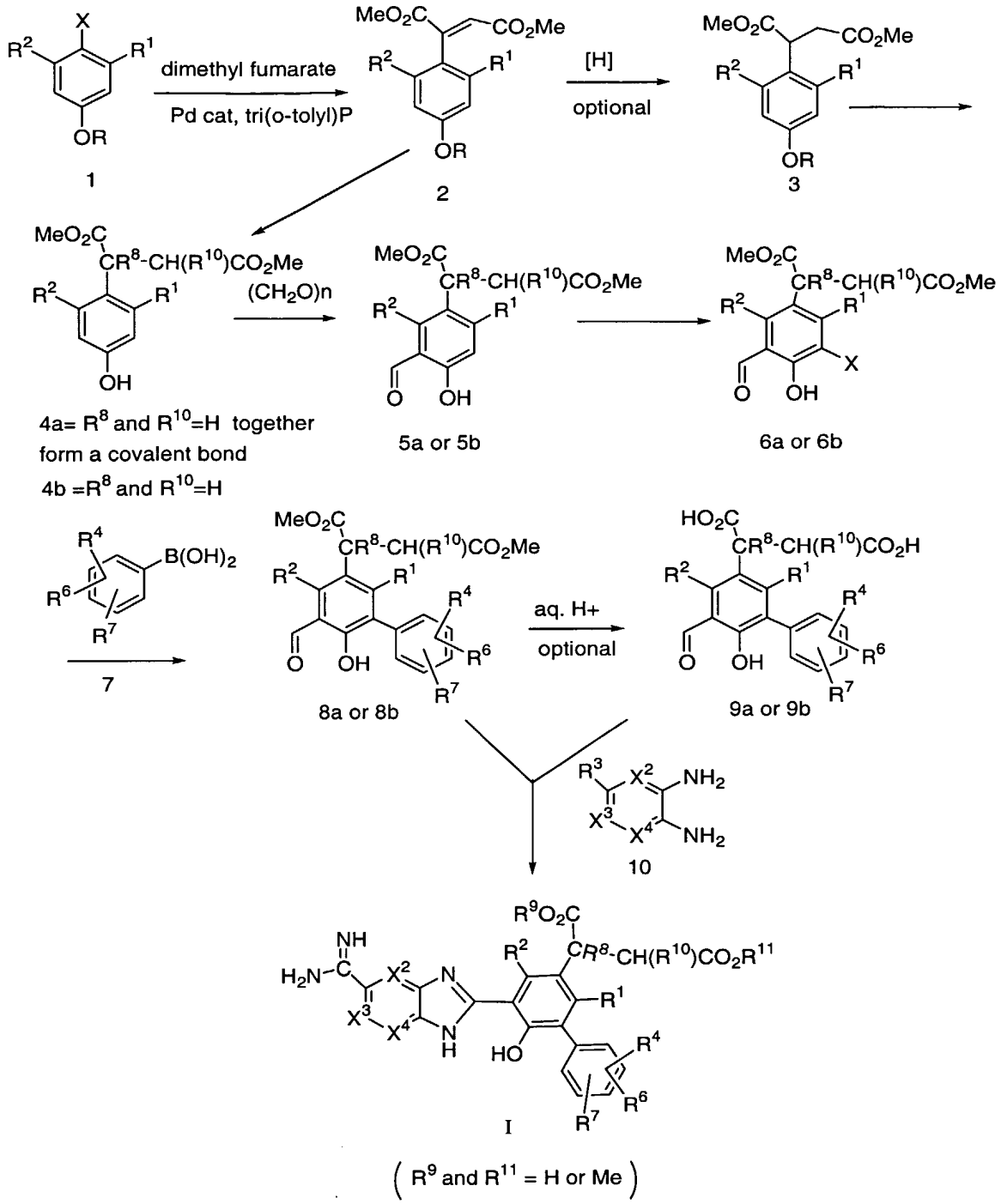
those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

Compounds of Formula I in which X^1 is –N-, R^3 is a group of formula (a) where n is 0, R^{13} is hydrogen and X^2, X^3, X^4, R^1, R^2, R^4-R^{11} are as defined in the Summary of the Invention can be prepared as described in Scheme I below.

Scheme I



Reaction of a phenol derivative of formula 1 where R is hydrogen, alkyl or other suitable oxygen protecting group, X is halo, and R^1 and R^2 are as defined in the Summary of the Invention with fumarate diester such as dimethyl fumarate in the presence of a palladium (II) catalyst such as palladium acetate and tri(o-tolyl)phosphine or triphenylphosphine provides a (E)-2-phenyl-but-2-enedioic acid dimethyl ester compound of formula 2. The

reaction is carried out in a suitable organic solvent such as acetonitrile, toluene, dimethylformamide, and the like, and in the presence of an organic base such as triethylamine, and the like.

Compounds of formula 1 are commercially available or they can be prepared by methods well known in the art. For example, 4-iodoanisole and 4-iodophenol are commercially available.

Compound 2 can be optionally reduced under hydrogenation reaction conditions to provide a 2-phenyl-succinic acid dimethyl ester compound of formula 3.

Compound 2 or 3 (where R is other than hydrogen) is then converted to the corresponding (E)-2-(4-hydroxyphenyl)-but-2-enedioic acid dimethyl ester (R^8 and R^{10} form covalent bond) or 2-(4-hydroxyphenyl)-succinic acid dimethyl ester (R^8 and R^{10} are hydrogen) compound of formula 4a or 4b respectively, by removal of the R group. The reaction conditions employed for the removal if R group depends on the nature of the R group. For example, if R is alkyl, it is removed by dealkylating agents such as hydrobromic acid, boron tribromide, and the like.

Treatment of 4a or 4b with paraformaldehyde under standard reaction conditions provides a (E)-2-(3-formyl-4-hydroxyphenyl)-but-2-enedioic dimethyl ester or 2-(3-formyl-4-hydroxyphenyl)-succinic acid dimethyl ester compound of formula 5a or 5b, respectively. Compound 5a or 5b is then converted to a compound of formula 6a or 6b where X is halo, preferably bromo or iodo with a suitable halogenating agent such as N-bromo succinimide, N-iodosuccinimide, and the like. The reaction is carried out in a suitable organic solvent such as dimethylformamide.

A compound of formula 6a or 6b is then treated with a phenyl boronic acid of formula 7 to provide a (E)-2-(5-formyl-6-hydroxybiphenyl-3-yl)-but-2-enedioic or 2-(5-formyl-6-hydroxybiphenyl-3-yl)-succinic acid dimethyl ester compound of formula 8a or 8b respectively, which can be optionally converted to the corresponding diacid compound of formula 9a or 9b under aqueous acidic or basic hydrolysis reaction conditions.

Alternatively, a compound of formula 6a or 6b can be converted to a boronic acid derivative by methods well known in the art and the resulting boronic acid can then be coupled with a halobenzene of the formula Ph(R^4, R^6, R^7)X where X is halo and R^4-R^7 are as defined in the Summary of the Invention under the conditions described above to provide a compound of formula 8a or 8b respectively.

A compound or formula 8(a or b) or 9(a or b) is then condensed with a 1,2-diamino compound of formula 10 to provide a compound of Formula I where X^1 is –N-. The reaction is

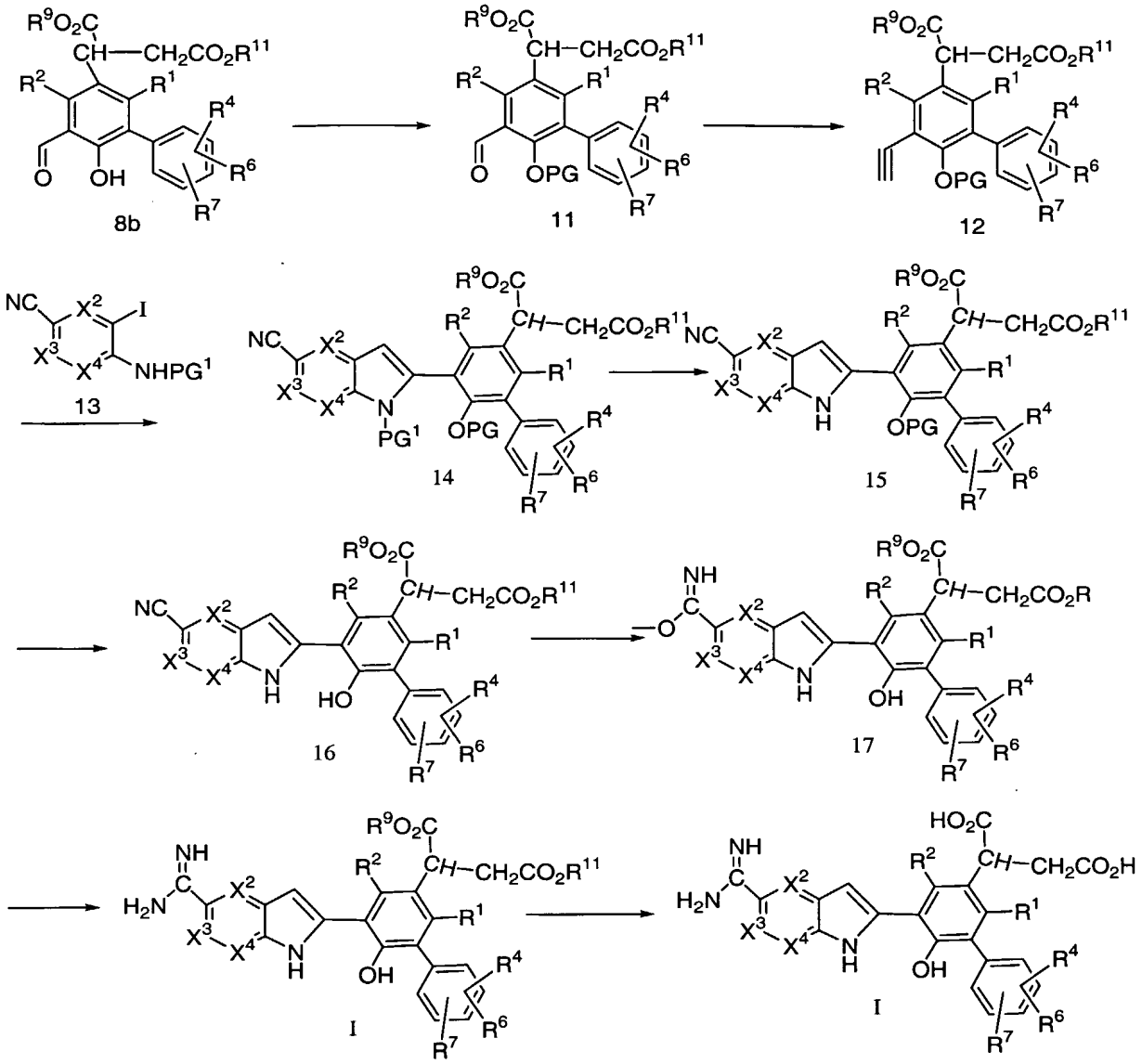
carried out in the presence of a suitable oxidant such as benzoquinone or air oxidation and in a suitable organic solvent such as ethanol, propanol, and the like.

Compounds of formula 10 are commercially available or they can be prepared by methods well known in the art. For example, 3,4-diaminobenzamidine can be readily prepared by methods well known in the art.

Compounds of Formula I can be converted to other compounds of Formula I. For example, a compound of Formula I where R^7 ureido can be prepared from a corresponding compound of Formula I where R^7 is nitro by reducing the nitro group to an amino group and then reacting the amino group with isocyanate.

Compounds of Formula I in which X^1 is –CH-, R^3 is a group of formula (a) where n is 0, R^{13} is hydrogen, and X^2, X^3, X^4, R^1, R^2, R^4-R^{11} are as defined in the Summary of the Invention can be prepared as described in Scheme II below.

Scheme II



Protection of the hydroxy group in a compound of formula 8a where R^9 and R^{11} are alkyl, prepared as described in Scheme I above, with a suitable hydroxy protecting group provides a compound of formula 11. A comprehensive list of suitable hydroxy protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. Preferred hydroxy protecting group is 2-methoxyethoxymethyl. The reaction is typically carried out in the presence of a base such as diisopropylethylamine, and the like and in a halogenated organic solvent such as dichloromethane, carbon tetrachloride, chloroform, and the like.

Ethynylation of 11 utilizing a modified procedure described in Muller, S.; Liepold , B.; Roth G. J.; Bestmann H.J. *Synlett* **1996**, *6*, 521-522 provides a 2-(5-ethynylbiphenyl-3-yl)-

succinic acid dialkyl ester compound of formula 12. A detailed description of this procedure is provided in working examples below.

Reaction of a compound of formula 11 with a 4-cyanoaniline compound of formula 13 where PG^1 is a suitable nitrogen protecting group such as methylsulfonyl, tert-butoxycarbonyl, trifluoroacetyl, and the like, utilizing the reaction conditions described in Sakamoto, T; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305 provides 2-[5-(5-cyanoindol-2-yl)biphenyl-3-yl]-succinic acid dialkyl ester compound of formula 14. Deprotection of the amino group in 14 provides a 2-[5-(5-cyano-1H-indol-2-yl)biphenyl-3-yl]-succinic acid dialkyl ester compound of formula 15. The reaction conditions utilized in the deprotection step depends on the nature of the nitrogen protecting group. For example, if the protecting group is methylsulfonyl it is removed under basic hydrolysis reaction conditions. Suitable bases are aqueous sodium hydroxide, potassium hydroxide, and the like. The reaction is carried out in an alcoholic solution such as methanol, ethanol, and the like. If the protecting group is *tert*-butoxycarbonyl it is removed under acidic hydrolysis reaction conditions. Compounds of formula 13 are either commercially available or they can be prepared by methods well known in the art.

The hydroxy-protecting group in 15 is then removed to provide 2-[5-(5-cyanoindol-2-yl)-6-hydroxybiphenyl-3-yl]-succinic acid dialkyl ester 15. The reaction conditions employed for the deprotection reaction depend on the nature of the hydroxy protecting group. For example, if the protecting group is 2-methoxyethoxymethoxy, it is removed by treating 15 with an acid under non-aqueous reaction conditions, in a suitable alcoholic solvent.

The cyano group in compound 16 is then converted into the amidino group by first treating 16 with hydrogen chloride gas in an anhydrous alcoholic solvent such as methanol, ethanol and the like, and then treating the resulting 2-[5-(5-methoxycarbonimidolyl-1H-indol-2-yl)-6-hydroxybiphenyl-3-yl]-succinic acid dialkyl ester 17 with an inorganic base such as ammonium carbonate or excess ammonia in an alcoholic solvent such as methanol, ethanol, and the like to give resulting 2-[5-(5-carbamimidolyl-1H-indol-2-yl)-6-hydroxybiphenyl-3-yl]-succinic acid dialkyl ester of Formula I. 2-[5-(5-Carbamimidolyl-1H-indol-2-yl)-6-hydroxybiphenyl-3-yl]-succinic acid dialkyl ester of Formula I can be converted to a corresponding compound of Formula I where R^9 and R^{11} are hydrogen under hydrolysis conditions well known in the art.

The above procedure can also be used to prepare compounds of Formula I where R^8 and R^{10} together form a covalent bond. The compounds of Formula I can also be prepared by synthetic procedures described in Applicant's PCT Application Publication No. WO 00/35886 the disclosure of which is incorporated herein by reference in its entirety.

Utility

The compounds of this invention inhibit Factors VIIa, IXa, Xa, and XIa, in particular Factor VIIa, and are therefore useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis), and systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of reocclusion (i.e., thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of rethrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment when blood is in contact with foreign surfaces in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, septic shock, septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease and the formation of atherosclerotic plaques, cerebral arterial disease, cerebral infarction, cerebral thrombosis, cerebral embolism, peripheral arterial disease, ischaemia, angina (including unstable angina), reperfusion damage, restenosis after percutaneous transluminal angioplasty (PTA) and coronary artery bypass surgery. Compounds of Formula I or II can also be used for treating cancer.

Testing

The ability of the compounds of this invention to inhibit factor VIIa and Xa can be tested *in vitro* and *in vivo* assays described in biological assays Example 1 and 2 below.

Administration and Pharmaceutical Compositions

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of Formula I may range from approximately 0.01-50 mg per kilogram body weight of the recipient per day; preferably about 0.1-20 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 7 mg to 1.4 g per day.

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral or parenteral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Oral compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the

compound of Formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of Formula I based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations containing a compound of Formula I or II are described below.

The compounds of Formula I or II can be administered alone or in combination with other compounds of Formula I or II in combination with one or more other active ingredient(s). For example, a compound of Formula I can be administered in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, a factor IXa, and a factor Xa inhibitor. Preferably, the thrombin inhibitor is Inogatran®, Melagatran® or prodrugs thereof which are disclosed in PCT Application Publication Nos. WO 94/29336 and WO 97/23499, the disclosures of which are incorporated herein by reference in their entirety. Factor Xa inhibitors that may be used in the combination products according to the invention include those described in *Current Opinion in Therapeutic Patents*, 1993, 1173-1179 and in international patent applications WO 00/20416, WO 00/12479, WO 00/09480, WO 00/08005, WO 99/64392, WO 99/62904, WO 99/57096, WO 99/52895, WO 99/50263, WO 99/50257, WO 99/50255, WO 99/50254, WO 99/48870, WO 99/47503, WO 99/42462, WO 99/42439, WO 99/40075, WO 99/37304, WO 99/36428, WO 99/33805, WO 99/33800, WO 99/32477, WO 99/32454, WO 99/31092, WID 99/26941, WO 99/26933, WO 99/26932, WO 99/26919, WO 99/26918, WO 99/25720, WO 99/16751, WO 99/16747, WO

99/12935, WO 99/12903, WO 99/11658, WO 99/11617, WO 99/10316, WO 99/07732, WO 99/07731, WO 99/05124, WO 99/00356, WO 99/00128, WO 99/00127, WO 99/00126, WO 99/00121, WO 98/57951, WO 98/57937, WO 98/57934, WO 98/54164, WO 98/46591, WO 98/31661, WO 98/28282, WO 98/28269, WO 98/25611, WO 98/24784, WO 98/22483, WO 98/16547, WO 98/16525, WO 98/16524, WO 98/16523, WO 98/15547, WO 98/11094, WO 98/07725, WO 98/06694, WO 98/01428, WO 97/48706, WO 97/46576, WO 97/46523, WO 97/38984, WO 97/30971, WO 97/30073, WO 97/29067, WO 97/24118, WO 97/23212, WO 97/21437, WO 97/08165, WO 97/05161, WO 96/40744, WO 96/40743, WO 96/40679, WO 96/40100, WO 96/38421, WO 96/28427, WO 96/19493, WO 96/16940, WO 95/28420, WO 94/13693, WO 00/24718, WO 99/55355, WO 99/51571, WO 99/40072, WO 99/26926, WO 98/51684, WO 97/48706, WO 97/24135, WO 97/11693, WO 00/01704, WO 00/71493, WO 00/71507, WO 00/71508, WO 00/71509, WO 00/71511, WO 00/71512, WO 00/71515, WO 00/71516, WO 00/13707, WO 00/31068, WO 00/32590, WO 00/33844, WO 00/35859, WO 00/35886, WO 00/38683, WO 00/39087, WO 00/39092, WO 00/39102, WO 00/39108, WO 00/39111, WO 00/39117, WO 00/39118, WO 00/39131, WO 00/40548, WO 00/40571, WO 00/40583, WO 00/40601, WO 00/47207, WO 00/47553, WO 00/47554, WO 00/47563, WO 00/47578, WO 00/51989, WO 00/53264, WO 00/59876, WO 00/59902, WO 00/71510, WO 00/76970, WO 00/76971, WO 00/78747, WO 01/02356, WO 01/02397, WO 01/05784, WO 01/09093, WO 01/12600, WO 01/19788, WO 01/19795, WO 01/19798, WO 93/15756, WO 94/17817, WO 95/29189, WO 96/18644, WO 96/20689, WO 96/39380, WO 97/22712, WO 97/36580, WO 97/36865, WO 97/48687, WO 98/09987, WO 98/46626, WO 98/46627, WO 98/46628, WO 98/54132, WO 99/07730, WO 99/33458, WO 99/37643 and WO 99/64446; in US patents Nos. 6,034,093, 6,020,357, 5,994,375, 5,886,191, 5,849,519, 5,783,421, 5,731,315, 5,721,214, 5,693,641, 5,633,381, 5,612,378, 6,034,127, 5,670,479, 5,658,939, 5,658,930, 5,656,645, 5,656,600, 5,639,739, 5,741,819, 6,057,342, 6,060,491, 6,080,767, 6,087,487, 6,140,351, 6,395,731, and 5,646,165; in Japanese patent applications Nos. JP 99152269, JP 10017549, JP 10001467, JP 98017549, JP 00178243, JP 11140040, JP 12143623, JP 12204081, JP 12302765, JP 6327488 and JP 98001467; in European patent applications EP 937 723, EP 937 711, EP 874 629, EP 842 941, EP 728 758, EP 540 051, EP 419 099, EP 686 642, EP 1 016 663 and EP 529 715; and in German patent applications Nos. DE 19845153, DE 19835950, DE 19743435, DE 19829964, DE 19834751, DE 19839499, DE19900355, DE19900471 and DE 19530996, the specific and generic disclosures in all of which documents are hereby incorporated by reference.

Factor Xa inhibitors also include those disclosed in international patent applications WO 96/10022, WO 97/28129, WO 97/29104, WO 98/21188, WO 99/06371, WO 99/57099,

WO 99/57112, WO 00/47573, WO 00/78749, WO 99/09027 and WO 99/57113, the specific and generic disclosures in all of which documents are hereby incorporated by reference, as well as 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl]phenyl}-pyridine-1-oxide and pharmaceutically acceptable derivatives thereof. Preferred Factor Xa inhibitors include antistatin, tick anticoagulant protein and those known as SQ-311 and SQ-315 (see international patent application WO 98/57951); SN-292 (see international patent application WO 98/28282); SN-429 and SN 116 (see international patent application WO 98/28269); RPR-208707 (see international patent application WO 98/25611 at Example 48); XU-817 (see international patent application WO 98/01428); SF-324 and SF-303 (see international patent application WO 97/23212); YM 60828 (see international patent application WO 96/16940 at Example 75); FACTOREX (see US patent No. 5,783,421); SF-324 (see European patent application EP 874 629); DX9065A (see European patent application EP 540 051 at Example 39); 1-(4-amidinobenzyl)-4-(6-chloronaphthalene-2-ylsulfonyl)piperazin-2-one (see JP 12204081 at Example 2); M55555 (see international patent application WO 99/33805 at Example 39); DPC423 (l-(3-amidinopheny1)-2-(2'-aminolsulfonyl[l, l'-biphenyl]-4-ylaminocarbonyl)-4-bromopyrrole, see international patent application WO 98/28269); 3-(3,5-difluoro-6-[3-(4,5dihydro-l-methylimidazol-2-yl)phenoxy]-4-[2,3-dihydroxy-propoxy]-pyridin-2-yloxy)-4-hydroxybenzamidine (see international patent application WO 00/31068); ZK-807834 (see international patent application WO 7/29067); 1,4-diaza-4-(6-chloro-naphthalene-2ylsulfonyl)-6-(methoxymethyl)-7-oxa-l'-(pyridin-4-yl)spiro[bicyclo[4-3.0]-nonane-8,4'-piperidine]-2-one (see international patent application WO 01/02397); (S)-l-(4-aminoquinazolin-7-ylmethyl)-4-[2-(5-chlorothien-2-yloxy)acetyl]-3-methoxymethylpiperazin-2-one (see international patent application WO 00/32590); 3-(2-[4-(2-aminosulfonyl-phenyl)benzoylphenoxy)benzamidine (see international patent application WO 01/19788); and 4-(2-[4-(5-chloroindol-2-ylsulfonyl)-2-(pyrrolidin-l-ylcarbonylmethyl)piperazin-1-ylcarbonyl]-thiazol-5-yl)pyridine N-oxide (see Japanese patent application No. JP 12143623); as well as the compounds of Example 7 of international patent application WO 98/21188, of Examples 3 and 6 of WO 99/57113, of Example 6 of international patent application WO 00/78747, of Examples 188, 211 and 167 of US patent No. 6,080,767, of Examples 40, 54 and 55 of international patent application WO 99/33805, of Examples 5, 6, 8, 9, 10, 11, 12, 13, 15, 16 and 17 of international patent application WO 01/05784, of Examples 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 22, 23, 25, 26, 28, 29, 30, 31, 32, 33, 34, 38, 39, 40, 41, 42 and 43 of international patent application WO 01/12600, and of Examples 802 and 877 of international patent application WO 00/35886. Other anticoagulant agents that can be used in the combination therapy are those disclosed in U.S. Patent Applications Publication Nos.

20020065303, 20020061842, 20020058677, 20020058657, 20020055522, 20020055469, 20020052368, 20020040144, 20020035109, 20020032223, 20020028820, 20020025963, 20020019395, 20020019394,20020016326, 20020013314, 20020002183, 20010046974, 20010044537, 20010044536, 20010025108, 20010023292, 20010023291, 20010021775, 20010020020033, 20010018423, 20010018414, and 20010000179, which are incorporated herein by reference in their entirety.

Suitable formulations for use in administering melagatran and derivatives (including prodrugs) thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912, WO 99/27913, WO 00/12043 and WO 00/13671, the disclosures in which documents are hereby incorporated by reference.

Similarly, suitable formulations for use in administering Factor Xa inhibitors and derivatives (including prodrugs) thereof are described in the literature, for example as described in the prior art documents relating to Factor Xa inhibitors that are mentioned hereinbefore, the disclosures in which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations, and in particular combined preparations including both melagatran/derivative and Factor Xa inhibitor/derivative may be achieved non-inventively by the skilled person using routine techniques. The amounts of melagatran, Factor Xa inhibitor, or derivative of either, in the respective formulation(s) will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

Suitable doses of melagatran, Factor Xa inhibitors and derivatives of either, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the prior art documents relating to melagatran (or derivatives (including prodrugs) thereof), and to Factor Xa inhibitors, that are mentioned hereinbefore, the disclosures in which documents are hereby incorporated by reference.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Synthetic Examples

REFERENCE 1

Synthesis of 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-succinic acid dimethyl ester

Step (a)

A solution of 1-iodo-4-methoxy-benzene (48.4 g, 0.207 mol) in acetonitrile (55 mL) was mixed with triethylamine (29.0 mL, 0.207 mol), $Pd(OAc)_2$ (0.264 g, 2.07 mmol) and tri(*o*-tolyl)phosphine (1.26 g, 4.14 mmol) followed by (E)-but-2-enedioic acid dimethyl ester (42.44 mL, 0.26 mol). The resulting mixture was refluxed for three hours and then was combined with water/ether. The mixture was extracted with ether (x2) and the extract dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by column chromatography (600 g silica/EtOAc/hexane) to yield (E)-2-(4-methoxy-phenyl)-but-2-enedioic acid dimethyl ester (87% yield).

Step (b)

A solution of (E)-2-(4-methoxy-phenyl)-but-2-enedioic acid dimethyl ester (12.5 g, 45 mmol) in ethanol (250 mL) was mixed with Pearlman's catalyst (400 mg) and the resulting mixture was hydrogenated from approximately 15 hours. The reaction mixture then was filtered through silica and the ethanol filtrate was concentrated under reduced pressure to yield 2-(4-methoxy-phenyl)-succinic acid dimethyl ester (99% yield).

Step (c)

A mixture of 2-(4-methoxy-phenyl)-succinic acid dimethyl ester (30.0 g, 0.107 mol) and 48% aqueous HBr (250 ml) was heated for 4 hours at 120 °C. The mixture was concentrated under reduced pressure. The residue was mixed with methanol (500 mL) and then thionyl chloride (10 mL). The mixture was heated approximately 4 hours at a temperature of approximately 60°C. The mixture was concentrated and the residue was mixed with aqueous sodium bicarbonate. The aqueous mixture was extracted with methylene chloride (x3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 2-(4-hydroxy-phenyl)-succinic acid dimethyl ester (92% yield).

Step (d)

A mixture of 2-(4-hydroxy-phenyl)-succinic acid dimethyl ester (11.90 g, 50.0 mmol) and dry acetonitrile (250 mL) was treated with anhydrous magnesium chloride (7.14 g, 75.0 mmol), TEA (26.13 mL, 0.1875 mol) and paraformaldehyde (10.51 g, 0.35 mol). The reaction mixture was refluxed for approximately 1 hour, cooled to ambient temperature and mixed with 1N HCl/ether. The organic layer was isolated and the aqueous layer was extracted with ether (x2). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. A mixture of the residue and dry acetonitrile (250 mL) was treated with

anhydrous magnesium chloride (7.14 g, 75.0 mmol), TEA (26.13 mL, 0.1875 mol) and paraformaldehyde (10.51 g, 0.35 mol). The reaction mixture was refluxed for approximately 1 hour, cooled to ambient temperature and mixed with 1N HCl/ether. The organic layer was isolated and the aqueous layer was extracted with ether (x2). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 2-(3-formyl-4-hydroxy-phenyl)-succinic acid dimethyl ester (89% yield).

Step (e)

A mixture 2-(3-formyl-4-hydroxy-phenyl)-succinic acid dimethyl ester (15.3 g, 57.45 mmol) and dry DMF (150 mL) was diluted, in a drop wise manner, with a solution of *N*-bromosuccinimide (NBS, 11.3 g, 63.5 mmol) in DMF (75 mL). The mixture was agitated for about 2 hours and then concentrated under reduced pressure at less than 35°C. The residue was dissolved in ether and the mixture was washed with water (x3). The ether layer was dried ($MgSO_4$) and then concentrated to yield 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-succinic acid dimethyl ester (99% yield).

^{1}H NMR ($CDCl_3$) δ: 2.57 (d of d, J = 6 Hz, 18 Hz, 1H), 3.04 (d of d, J = 11 Hz, 18 Hz, 1H), 3.54 (s, 3H), 3.57 (s, 3H), 3.93 (d of d, J = 6 Hz, 11 Hz, 1H), 7.35 (d, J = 2 Hz, 1H), 7.59 (d, J = 2 Hz, 1H), 9.70 (s, 1H), 11.41 (s, 1H). MS: found (MH+) 345.0, calc 344.99.

REFERENCE 2

Synthesis of (*E*)-2-(3-formyl-4-hydroxy-5-iodo-phenyl)-but-2-enedioic acid dimethyl ester

Step (a)

A 1L 24/40 round bottom flask was charged with 4-iodophenol (18.46 g, 83.9 mmol), dimethyl fumarate (13.30 g, 82.30 mmol), tri-*O*-tolylphosphine (510 mg, 1.68 mmol), triethylamine (200mL) and a magnetic stir bar. The reaction flask was sparged with nitrogen, sealed with a rubber septum and kept under an atmosphere of nitrogen throughout the reaction. The reaction mixture was heated at 90 °C until all solids had dissolved and then palladium acetate (189 mg, 0.84 mmol) was added to the solution. The reaction mixture was stirred with heating for 18 hours and then stripped to a solid. The solid was combined with ethyl acetate (1L) which to give a suspension. The suspension was washed with 1N aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, filtered and concentrated to give a gum (15.9 g). The residue was triturated with 1:1 ethyl acetate: hexanes to give (*E*)-2-(4-hydroxy-phenyl)-but-2-enedioic acid dimethyl ester (7.9 g, 33 mmol, 40% yield).

Step (b)

A 1L 24/40 round bottom flask was charged with (*E*)-2-(4-hydroxyphenyl)-but-2-enedioic acid dimethyl ester (4.78 g, 20.24 mmol), acetonitrile (200 mL), $MgCl_2$ (2.89 g, 30.35 mmol), triethylamine (11 mL, 75.88 mmol) and a magnetic stir bar. The mixture was stirred and warmed to 50 °C and then paraformaldehyde (4.10 g, 136.59 mmol) was added to the mixture. The mixture was heated to reflux, stirred for 2 hours, then cooled to ambient temperature and poured into 1L diethyl ether. The resulting mixture was washed with 1N hydrochloric acid, dried over $MgSO_4$, filtered and concentrated to an oil. The oil was combined with acetonitrile (200 mL), $MgCl_2$ (2.89 g, 30.35 mmol) and triethylamine (11 mL, 75.88 mmol) in a 1L 24/40 round bottom flask with a magnetic stirring bar. The mixture was stirred and warmed to 50 °C and then paraformaldehyde (4.10 g, 136.59 mmol) was added to the mixture. The mixture was heated to reflux, stirred for 2 hours, then cooled to ambient temperature and poured into 1L diethyl ether. The resulting mixture was washed with 1N hydrochloric acid, dried over $MgSO_4$, filtered and concentrated to give (*E*)-2-(3-formyl-4-hydroxy-phenyl)-but-2-enedioic acid dimethyl ester (4.0 g, 15.14 mmol).

Step (c)

A 1L round bottom flask was charged with (*E*)-2-(3-formyl-4-hydroxy-phenyl)-but-2-enedioic acid dimethyl ester (4.0 g, 15.14 mmol), DMF (100 ml) and a magnetic stir bar and fitted with an addition funnel. *N*-Iodosuccinimide (5.11g, 22.71mmol) in DMF was added dropwise via the addition funnel. The mixture was stirred for 2 hours and then was diluted with diethyl ether (500 mL). The resulting mixture was washed with water, dried over $MgSO_4$, filtered and concentrated to a dark solid. The residue was triturated with diethyl ether to give (*E*)-2-(3-formyl-4-hydroxy-5-iodo-phenyl)-but-2-enedioic acid dimethyl ester (3.0 g, 7.7 mmol, 51% yield) as a light yellow waxy solid. MS LCMS Q^- 388.960 (calc.), 389.1 (obs.), Q^+ 390.968 (calc.).

REFERENCE 3

Synthesis of 2-(5-formyl-6-hydroxy-3'-nitro-biphenyl-3-yl)-succinic acid

Step (a)

A mixture of 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-succinic acid dimethyl ester (15.0 g, 43.5 mmol), prepared as in Reference 1 above, toluene (220 mL) and methanol (90 mL) was combined with 3-nitrophenylboronic acid (10.9 g, 65.3 mmol) and 2M aqueous sodium carbonate (33.0 mL, 66.0 mmol). The reaction flask was flushed with nitrogen and the reaction mixture then was mixed with tetrakis-(triphenyl phosphine) palladium (5.1 g, 4.4 mmol) and the mixture was heated to reflux for about 7 hours. The mixture was cooled to

ambient temperature and then mixed with 1M HCl. The organic layer was isolated, dried ($MgSO_4$) and evaporated. The residue was purified using column chromatography (300 g silica, EtOAc/hexane) to give 2-(5-formyl-6-hydroxy-3'-nitro-biphenyl-3-yl)-succinic acid dimethyl ester (66% yield).

Step (b)

A mixture of 2-(5-formyl-6-hydroxy-3'-nitro-biphenyl-3-yl)-succinic acid dimethyl ester (3.8 g, 10 mmol), 3N aqueous HCl (60 mL) and acetonitrile (20 mL) was heated for approximately 4 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure. The residue was dried over phosphorus pentoxide under high vacuum to yield 2-(5-formyl-6-hydroxy-3'-nitro-biphenyl-3-yl)-succinic acid (98% yield). MS: found (M-H) 358.1, calc 359.06.

REFERENCE 4

Synthesis of 2-[5-ethynyl-6-(2-methoxyethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester

Step (a)

A mixture of 2-(5-formyl-6-hydroxy-3'-nitrobiphenyl-3-yl)succinic acid dimethyl ester (0.80 g, 2.06 mmol), prepared as in Reference 3, Step (a), dichloromethane (35 mL) and diisopropylethylamine (0.72 mL, 4.12 mmol) was cooled to approximately 5° C. The cooled mixture was diluted by a drop wise addition of MEM-chloride (0.35 mL, 3.09 mmol) and the resulting mixture was warmed to ambient temperature. The mixture then was agitated at ambient temperature from approximately 15 hours and then mixed with ethyl acetate and water. The organic layer was isolated, washed with water (x5), dried ($MgSO_4$) and concentrated under reduced pressure to afford 2-[5-formyl-6-(2-methoxyethoxymethoxy)-3'-nitrobiphenyl-3-yl]succinic acid dimethyl ester.

Step (b)

A mixture of 2-[5-formyl-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester, methanol (12 mL), (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester (0.63 g 3.3 mmol), and finely ground potassium carbonate (0.85 g, 6.18 mmol) was agitated for approximately 30 minutes. The progress of the reaction was followed by monitoring the evolution of nitrogen and when complete the reaction was quenched by the addition of 5% citric acid. The mixture was extracted with ethyl acetate and the organic layer was passed through a pad of silica using 40% EtOAc/hexane as eluent. The organic layer was concentrated under reduced pressure to afford the compound of 2-[5-ethynyl-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester.

NMR ($CDCl_3$) δ: 2.67 (d of d, J=6.0 Hz, 18.7 Hz, 1H), 3.10-3.30 (m, 8H),3.67 (s, 3H), 3.69 (s, 3H) ,4.05 (d of d, J=6.0 Hz, 10.7 Hz, 1H), 5.07 (s, 2H), 7.24-7.31 (m, 2H), 7.44 (d, J=2.4 Hz, 1H), 7.58 (t, J= 9.0Hz,1H), 7.77-7.84 (m, 1H),8.19 (d of d, J=2.4 9.0 Hz, 1H), 8.37 (t, J=1.9Hz, 1H).

REFERENCE 5

Synthesis of 6-bromo-5-(*tert*-butoxycarbonylamino)-3-chloro-2-cyano-pyridine

Step (a)

2-Hydroxy-5-nitropyridine (50 g, 357 mmol) and *N*-chlorosuccinimide (55 g, 410 mmol) were suspended in anhydrous DMF (150 mL). The reaction mixture was stirred at room temperature for 18 hours. The resulting homogeneous reaction mixture was dilluted by the slow addition of 750 mL of water, which resulted in the precipitation of the desired 3-chloro-5-nitro-2-hydroxypyridine as a pale yellow powder. The solids were isolated via filtration and further dried under high vacuum to provide 3-chloro-5-nitro-2-hydroxypyridine (59 g, 95% yield).

Step (b)

3-Chloro-5-nitro-2-hydroxy-pyridine (20 g) was added in small portions to thionylchloride (200 ml) under vigorous stirring. The suspension was heated to 100^0C within 1 h and stirred at 100^0C for 1 h. After cooling the solution to RT, the solvent was removed under reduced pressure, the residue dissolved in AcOEt, and washed with water (3 x 200 ml). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 2,3-dichloro-5-nitropyridine (18 g) as a pale yellow solid.

Step (c)

A solution of 2,3-dichloro-5-nitropyridine (9.75 g) and KI (29 g) in HOAc (120 ml, degassed with N_2) was heated to 100 °C for 1.5 h under N_2. The brown solution was cooled to room temperature, AcOEt (300 ml) added and the organic phase washed with water (2 times 100 ml) and dilute aqu. Na_2SO_3 (100 ml). Evaporation of the solvent gave crystalline 3-chloro-2-iodo-5-nitro-pyridine (13.11 g).

Step (d)

A suspension of CuCN (7 g, Caution! Toxic HCN may be formed!) and 3-chloro-2-iodo-5-nitro-pyridine (7 g, Caution! Compound may detonated at elevated temperatures) in acetonitrile (200 ml) was heated to 80 °C within 1 h and stirred at 80 °C for 5 h. Evaporation of the solvent and filtration of the residue in AcOEt over SiO_2 gave 3-chloro-2-cyano-5-nitro-pyridine (4.26 g).

Step (e)

A solution of $SnCl_2$ (52 g) and 3-chloro-2-cyano-5-nitro-pyridine (10.3 g) was stirred in AcOEt (200 ml) at room temperature for 10 min and at 70 °C for 4 h. The solution was cooled to room temperature, diluted with AcOEt (500 ml), $NaHCO_3$ (100 g) added in four portions within 4 h, and vigorously stirred for 20 h. The suspension was filtered, the filtrate washed with sat. aqu. $NaHCO_3$ solution and the solvent evaporated to give 5-amino-3-chloro-2-cyanopyridine (4.34 g) as an off-white powder.

Step (f)

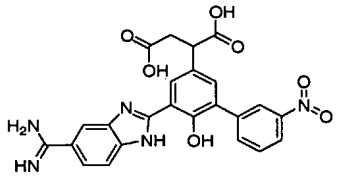
To a stirred solution of 5-amino-3-chloro-2-cyanopyridine (4.61 g) and NaOAc (4.81 g) in anhydrous AcOH (150 ml) at room temperature was added Br_2 (7.22 g). The solution was stirred at 60°C for 2 h. Evaporation of the solvent and excess bromine gave crude 5-amino-6-bromo-3-chloro-2-cyano-pyridine (7.27 g). Recrystallization from AcOEt afforded clean product (6.23 g).

Step (g)

5-Amino-6-bromo-3-chloro-2-cyano-pyridine (1.6 g) was dissolved in THF (5 ml) at room temperature. N, N-dimethylaminopyridine (0.5 g) followed by Boc_2O (3.78 g) in small portions was added and the solution stirred at room temperature for 30 min to give after removal of the solvent 6-Bromo-5-(bis-carbamic acid tert-butyl ester)-3-chloro-2-cyano-pyridine. The crude material was dissolved in dicloromethane (60 ml) and trifluoroacetic acid (1 g) added. The resulting solution was stirred for 1 h. The solvent was removed and the crude material purified by CC (AcOEt/hexane 1/1) to give 6-bromo-5-(*tert*-butoxycarbonylamino)-3-chloro-2-cyano-pyridine (1 g). MS (obs.): 333 (M + 1).

EXAMPLE 1

Synthesis of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid



A mixture of 2-(5-formyl-6-hydroxy-3'-nitro-biphenyl-3-yl)-succinic acid (0.3 g, 0.835 mmol), prepared as in Reference 3 above, 3,4-diaminobenzamidine mono hydrochloride (0.17 g, 0.9 mmol) and benzoquinone (0.097 g, 0.9 mmol) in 50 ml of ethanol was heated for approximately 4 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by reverse phase HPLC

(gradient, acetonitrile/0.02 N aqueous HCl) to yield 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid (63 % yield).

^{1}H NMR (DMSO-d_6) δ: 2.67 (d of d, J=18Hz, 6.0 Hz, 1H), 3.14 (d of d, J=18 Hz,11.5 Hz, 1H), 3.97 (d of d, J=6.0 Hz, 11.5 Hz, 1H), 7.54 (d, J=2.1 Hz, 1H), 7.70-7.86 (m,3H), 8.06 (d, J=8.8 Hz, 1H), 8.18-8.20 (m, 2H), 8.45 (t,J=2.1 Hz, 1H), 9.13 (br s, 2H), 9.40 (br s, 2H),

MS: found (M+H) 490.4, (M-H) 488.4, calc 489.13.

Proceeding as in Example I and substituting suitable starting materials provided the following compounds of Formula I:

2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6-hydroxy-3'-isopropyl-biphenyl-3-yl]-succinic acid hydrochloride salt; ^{1}H-NMR (d_6-DMSO) δ ppm: 9.35 (br s, 2H), 9.06 (br s, 2H), 8.16 (s, 1H), 8.07 (d, J= 2.2 Hz, 1H), 7.82 (d, J=9.3 Hz, 1H), 7.70 (d, J=10.2 Hz, 1H), 7.37 (m, 4H), 7.19 (d, J= 7.8 Hz, 1H), 3.92 (dd, J= 11.7, 5.7 Hz, 1H), 3.10 (m, 1H), 2.89 (m, 1H), 2.65 (dd, 15.9, 5.2 Hz, 1H), 1.20 (d, J= 7.6 Hz, 6H); LCMS Q^+ 487.19 (calc.), 487.7 (obs.), Q^- 485.19 (calc.), 485.4 (obs);

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid; ^{1}H-NMR (d_6-DMSO) δ ppm: 9.38 (br s, 2H), 9.10 (br s, 2H), 8.15 (s, 1H), 8.13 (s, 1H), 7.82 (d, J= 9.3 1H), 7.70 (d, J= 9.3 Hz, 1H), 7.64 (s, 1H), 7.54 (d, J= 9.3 Hz, 1H), 7.48-7.38 (m, 3H), 3.94 (dd, J=11.1, 5.4 Hz, 1H0, 3.12 (dd, 18.9, 11.2 Hz, 1H), 2.69-2.61 (m, 1H); MS LCMS Q^+ 479.10 (calc.), 479.2 (obs.), Q^- 477.10 (calc.), 477.3 (obs);

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methyl-biphenyl-3-yl]-succinic acid; ^{1}H-NMR (d_6-DMSO) δ ppm: 9.37 (bs, 2H), 9.09 (bs, 2H), 8.15 (s, 1H), 8.08 (d, J= 1.8, 1H), 7.81 (d, *J* = 9.3 Hz, 1H), 7.71 (d, *J* = 9.4 Hz, 1H), 7.36-7.25 (m, 4H), 7.13 (d, *J* = 6.0 Hz, 1H), 7.02 (m, 1H), 3.91 (dd, *J* = 10.2, 45.7 Hz, 1H), 3.10 (dd, J= 19.6, 11.2 Hz, 1H), 2.69-2.60 (m, 1H), 2.32 (s, 3H); MS LCMS Q^+ 459.16(calc.), 459.2(obs.), Q^- 457.16 (calc.), 457.2 (obs);

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2'-fluoro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-6-fluoro-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2',5'-dimethoxy-biphenyl-3-yl]-succinic acid;

2-[3'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-5'-nitro-biphenyl-3-yl]-succinic acid;

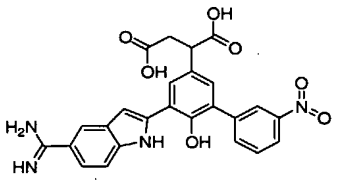
2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methyl-biphenyl-3-yl]-succinic acid; and

2-[2'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid.

EXAMPLE 2

Synthesis of 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid



Step (a)

A mixture of 2-[5-ethynyl-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (5.1 g, 10.8 mmol), prepared as in Reference 4, *N*-(4- cyano-2-iodo-phenyl)methanesulfonamide (3.5 g, 10.8 mmol), triethylamine (15.1 ml, 108 mmol), $Pd(Ph_3P)_2Cl_2$ (0.154 g, 0.22 mmol) and acetonitrile (150 ml) was agitated by bubbling with nitrogen gas for approximately 5 minutes and then combined with copper(I)iodide (0.041 g, 0.22 mmol). This mixture was heated to reflux for about 1hour, then cooled to ambient temperature and mixed with 5% citric acid. This mixture was extracted with DCM and the DCM layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica (eluent, hexane/ethyl acetate) to yield 2-[5-(5-cyano-1-methanesulfonyl-1*H*-indol-2-yl)-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (41% yield).

Step(b)

A mixture of 2-[5-(5-cyano-1-methanesulfonyl-1*H*-indol-2-yl)-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (2.93 g, 4.4 mmol), methanol (90 mL) and 50% aqueous NaOH (30 mL) was agitated at 50°C for approximately 2 hours. The mixture was cooled to ambient temperature and combined with 10% aqueous citric acid (excess). This mixture was extracted with ethyl acetate (x3) and the combined extracts were sequentially washed with water (x2) and brine (x1), dried ($MgSO_4$) and concentrated under reduced pressure to afford 2-[5-(5-cyano-1*H*-indol-2-yl)-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (99% yield).

MS : found (M+H) 559.4, calc 559.16.

Step (c)

A mixture of 2-[5-(5-cyano-1*H*-indol-2-yl)-6-(2-methoxy-ethoxymethoxy)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (2.5 g, 4.4 mmol), dry methanol (20 mL) and 4N HCl in dioxane (20 mL) was agitated at ambient temperature for approximately 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, 30 % EtOAc in hexane) to afford 2-[5-(5-cyano-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (64% yield).

MS: found (M+H) 500.4, (M-H) 498.4, calc 499.14.

Step (d)

A mixture of 2-[5-(5-cyano-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (1.3 g, 2.6 mmol) and dry methanol was cooled to about 0°C and then bubbled with dry HCl gas. This mixture was sealed in a reaction vessel, agitated at ambient temperature for approximately 24 hours and then bubbled with nitrogen gas. This mixture was concentrated under reduced pressure to afford 2-[6-hydroxy-5-(5-methoxycarbonimidoyl-1*H*-indol-2-yl)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester.

Step (e)

A mixture of 2-[6-hydroxy-5-(5-methoxycarbonimidoyl-1*H*-indol-2-yl)-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (1.5 g, 2.6 mmol) and methanol was combined with crystalline ammonium carbonate (excess) added in portions. This mixture then was agitated at ambient temperature for approximately 8 hours and then concentrated under reduced pressure. The residue was treated with aqueous 1N HCl forming a precipitate. The precipitate was isolated, washed with a minimum amount of 1N HCl and dried over P_2O_5 under high vaccum to yield 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (70% yield).

Step (f)

A mixture of 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid dimethyl ester (1 g, 1.8 mmol), 3.5 N aqueous HCl (60 mL) and acetonitrile (20 mL) was agitated at reflux conditions for approximately 1 hour. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (acetonitrile /0.02 N HCl gradient) to afford 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid (33% yield).
^{1}H NMR (DMSO-d_6) δ2.69 (d of d, J=6.0 Hz, 18.1 Hz, 1H), 3.25 (d of d, J=18. 1 Hz, 9.8 Hz, 1H), 3.98 (d of d, J= 6.0Hz, 9.8 Hz,1H), 7.17 (s, 1H), 7.28-8.40 (m, 9H)8.84 (br s, 2H), 9.19 (br s, 2H), 9.33 (s, 1H). MS: found (M+H) 489.2 , calc 488.13.

Proceeding as described in Example 2 above but starting with suitable starting material provided the following compounds of Formula I:

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid.

Biological Examples

EXAMPLE 1

In Vitro Factor VIIa Inhibitor Assay

Mixtures of human Factor VIIa (typically supplied at 7 nM) and test compound (present at varying concentrations) in assay medium (comprising: NaCl, 150 mM (pH 7.4); $CaCl_2$, 5 mM ; Tween-20, 0.05% ; Dade Innovin tissue factor [Dade Behring, Newark, DE, USA]; EDTA, 1.5 mM; and dimethylsulfoxide, 10 %) were incubated for 30 minutes at room temperature. Next, reactions were initiated with the addition of substrate [500 μM of CH_3SO_2-D-Cha-But-Arg-pNA (from Centerchem, Norwalk, CT, USA)]. Hydrolysis of the chromogenic substrate was followed spectrophotometrically at 405 nm for five minutes. Initial velocity measurements calculated from the progress curves by a kinetic analysis program (Batch Ki; BioKin, Ltd., Pullman, WA) were used to determine apparent inhibition constants (apparent K_i's).

Compounds of the invention tested by the above-described assay exhibited inhibition of Factor VIIa.

EXAMPLE 2

In Vitro Factor Xa Inhibitor Assay

Mixtures of human Factor Xa (typically supplied at 3 nM) (from Haematologic Technologies, Essex Junction, VT, USA) and test compound (varying concentrations) in assay medium (comprising: Tris, 50 mM (pH 7.4); NaCl, 150 mM; $CaCl_2$, 5 mM; Tween-20, 0.05%;

EDTA, 1mM; and dimethylsulfoxide, 10%) were incubated for 30 minutes at room temperature. Next, reactions were initiated with the addition of substrate [500 μM of CH_3CO_2-D-Cha-Gly-Arg-pNA (from Centerchem, Norwalk, CT, USA]. Hydrolysis of the chromogenic substrate was followed spectrophotometrically at (405 nm) for five minutes. Apparent inhibition constants (apparent K_i's) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention tested by the above-described assay exhibited inhibition of Factor Xa.

EXAMPLE 3

Pharmacokinetic Assay

Rats with pre-implanted jugular vein catheters, which were filled with heparin/saline/PVP lock prior to shipment, were bought from Charles River. Three rats were selected for each study, weighed, and injected with test compound by tail vein injection. Any residual test compound was retained and stored at -70 °C for later analysis.

Blood samples (0.25 mL each) were collected from the indwelling catheters at specified times over 120 hours. The catheters were flushed with physiological saline immediately after each collection and filled with heparinized saline after each 8, 24 and 48 hour collection. In the event that a catheter failed, blood samples were collected via the retro-orbital sinus under isoflurane anesthesia at the appropriate time.

Blood samples were placed in 0.5 mL Microtainer® tubes (lithium heparin), shaken gently and stored on wet ice. The samples were centrifuged for 10 minutes at 2400 rpm in a refrigerated centrifuged. Plasma samples (0.1 mL) from each tube were transferred to 0.5 mL Unison polypropylene vials (Sun - 500210) and stored below -70 °C for later analysis by LC/MS-MS.

EXAMPLE 4

In vitro Clotting Assays..... aPTT and PT

Coagulation assays, activated partial thromboplastin time (aPTT) and prothrombin time (PT) were carried out based on the procedure described in Hougie, C. *Hematology* (Williams, W. J., Beutler, B., Erslev, A. J., and Lichtman, M. A., Eds.), pp. 1766-1770 (1990), McGraw-Hill, New York.

Briefly, the assays were performed using normal human citrated plasma and were performed at 37 °C on a coagulometer (Electra 800) in accordance with the manufacturer's instructions (Medical Laboratory Automation- Pleasantville, New York). The instrument was

calibrated with plasma immediately prior to collecting clotting times for samples with inhibitors. The aPTT and PT doubling concentrations were calculated by fitting inhibitor dose response curves to a modified version of the Hill equation.

Pharmaceutical Composition Examples

The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g
sodium acetate buffer solution,	0.4 M 2.0 ml
HCl (1 N) or NaOH (1 N)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 ml

All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

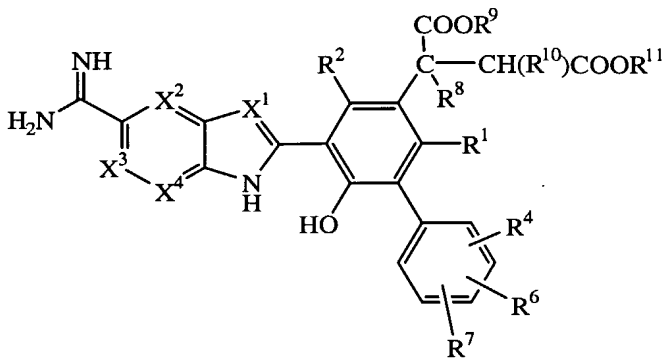
A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

WE CLAIM:

1. A compound of Formula I:



I

wherein:

X^1, X^2, X^3, and X^4 are independently –N- or -CR^5- wherein R^5 is hydrogen, alkyl, or halo with the proviso that not more than three of X^1, X^2, X^3 and X^4 are –N-;

R^1 and R^2 independently are hydrogen, alkyl, or halo;

R^4 is hydrogen, alkyl, alkylthio, halo, alkoxy, or nitro;

R^6 is hydrogen, alkyl, or halo;

R^7 is hydrogen, alkyl, halo, nitro, alkoxy, haloalkyl, carboxy, amino, alkylamino, dialkylamino, carbamimidoyl, alkylsulfonylamino, alkylthio, or ureido provided at least one of R^4, R^6 and R^7 is not hydrogen;

R^8 is hydrogen, hydroxy, or alkyl;

R^{10} is hydrogen or alkyl; or

R^8 and R^{10} together form a covalent bond;

R^9 and R^{11} are independently hydrogen or alkyl; and

individual isomers, mixture of isomers, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein when two of R^4, R^6 and R^7 are hydrogen, then the remaining of R^4, R^6 and R^7 is not located at the 4'-position of the phenyl ring with the carbon atom attaching the phenyl ring to the rest of the molecule being the 1'-position; and also when one of R^4, R^6 and R^7 is hydrogen, then the remaining of R^4, R^6 and R^7 are not simultaneously at the 3'- and 5'-position of the phenyl ring.

3. The compound of Claim 2 wherein X^1 is –N- and X^2, X^3, and X^4 are –CR^5- where R^5 is hydrogen.

4. The compound of Claim 2 wherein X^1 is –N-; X^2 and X^4 are –CR^5- where R^5 is hydrogen and X^3 is –CR^5- where R^5 is halo.

5. The compound of Claim 2 wherein X^1 is –C- and X^2, X^3, and X^4 are $-CR^5-$ where R^5 is hydrogen.

6. The compound of Claim 2 wherein X^1 is –C-; X^2 and X^4 are $-CR^5-$ where R^5 is hydrogen and X^3 is $-CR^5-$ where R^5 is halo.

7. The compound of Claim 3 wherein R^1, R^2, R^8 and R^{10} are hydrogen; and R^9 and R^{11} are hydrogen or ethyl.

8. The compound of Claim 4 wherein R^1, R^2, R^8 and R^{10} are hydrogen; and R^9 and R^{11} are hydrogen or ethyl.

9. The compound of Claim 7 wherein R^4 and R^6 are hydrogen and R^7 is located at the 3'-position of the phenyl ring.

10. The compound of Claim 9 wherein R^7 is nitro or halo.

11. The compound of Claim 10 wherein R^7 is nitro.

11. The compound of Claim 8 wherein R^4 and R^6 are hydrogen and R^7 is located at the 3'-position of the phenyl ring.

12. The compound of Claim 11 wherein R^7 is nitro or halo.

13. The compound of Claim 12 wherein R^7 is nitro.

14. A compound selected from the group consisting of:

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-isopropyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-methyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',3',5'-trichloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-chloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2'-fluoro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6-hydroxy-2'-methoxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2',5'-dimethoxy-biphenyl-3-yl]-succinic acid;

2-[3'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methoxy-5'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-nitro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methyl-biphenyl-3-yl]-succinic acid;

2-[2'-amino-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',5'-dichloro-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',6-dimethoxy-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2'-methoxy-6-hydroxy-5'-isopropyl-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methylthio-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2',3'-dichloro-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-chloro-5'-fluorobiphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3',5'-difluoro-biphenyl-3-yl]-succinic acid;

2-[5'-bromo-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-methylthio-biphenyl-3-yl]-succinic acid;

2-[3'-amino-5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-ureido-biphenyl-3-yl]-succinic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3',4'-dimethyl-biphenyl-3-yl]-succinic acid;

diethyl 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinate;

dimethyl 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinate;

2-[5-(5-carbamimidoyl-6-fluoro-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-nitro-biphenyl-3-yl]-succinic acid; and

(Z)-2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6-hydroxy-2'methoxy-biphenyl-3-yl]-but-2-enedioic acid; or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 12.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 14.

18. A method for treating a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

19. A method for treating a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 12.

20. A method for treating a thromboembolic disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 14.

21. A method of treating a a thromboembolic disorder, which method comprises administering to said animal a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1 in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, a factor IXa, and a factor Xa inhibitor.

22. Use of a compound of Formula I in the preparation of a medicament for use in the treatment of a thromboembolic disorder in an animal.

5

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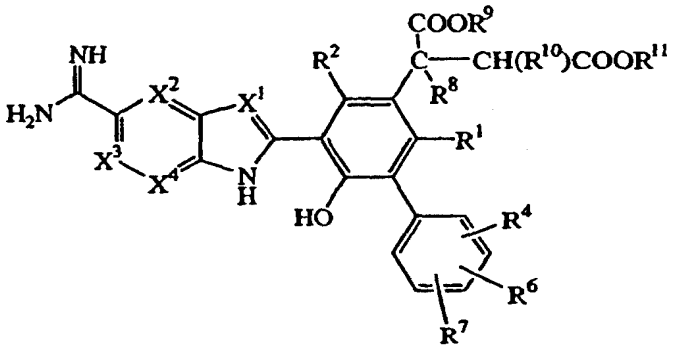
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 2-[5-(5-CARBAMIMIDOYL-1H-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL]-SUCCINIC ACID DERIVATIVES AS FACTOR VIIA INHIBITORS



(I)

(57) Abstract: The present invention relates to novel inhibitors of formula (I) of Factors VIIa, IXa, XIa, in particular Factor VIIa, pharmaceutical compositions comprising these inhibitors, and methods for using these inhibitors for treating or preventing thromboembolic disorders. Processes for preparing these inhibitors are also disclosed.

WO 03/006670 A3

INTERNATIONAL SEARCH REPORT

PCT/US 02/21340

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/404 A61K31/4184 A61P7/02 C07D235/18 C07D209/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 35886 A (AXYS PHARMACEUTICALS, INC., USA) 22 June 2000 (2000-06-22) claims; examples 178,179,182,186,445,446 see compounds (18),(19) page 134	1-22
P,A	YOUNG, W. B. ET AL: "Optimization of a screening lead for factor VIIa/TF" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(17), 2253-2256, 3 September 2001 (2001-09-03), XP002212336 the whole document	1-22
P,A	WO 02 14307 A (AXYS PHARMACEUTICALS, INC., USA) 21 February 2002 (2002-02-21) the whole document	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2003	28/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/US 02/21340

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US 02/21340

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